

Modeling neoadjuvant radiotherapy for improving treatments efficacy

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Purpose:

Neoadjuvant radiotherapy (RT) is considered as a key actor in many treatments and aims at improving tumor local control and patient overall survival. In many cases the RT schedule and the timing of surgery are mostly empirical and dependent upon the presence of side effects. Here, we propose to develop a pre-clinical model that mimics neoadjuvant RT. This pre-clinical model allows studying the impact of different neoadjuvant RT schedules on tumor microenvironment, tumor dissemination and helps for determining the best timing for surgery.

Methods:

We inject, subcutaneously, MDA-MB231 cell line into the flank of SCID mice. The tumors arising at the injection site are treated with “neoadjuvant RT” at a total dose and dose per fraction of 10Gy/2Gy and 10Gy/5Gy. The tumors are resected carefully at 4 or 11 days after the end of RT. The mice are sacrificed 45 days after the start of RT. Lungs, brain, liver and lymph nodes are collected to count metastatic deposit highlighted by human KI-67 labeling. At the time of surgery, we study different molecular pathways known to influence tumor dissemination: HIF-1alpha, TIMP-1 and 2, PAI-1, MT-1-MMP and MMP 2 and 9 with PCR and zymography. Cytokine arrays are used to determine inflammatory profile into the blood and into the tumor.

Results:

After the accomplishment of the whole procedure, we observe less than 10% mortality, demonstrating the feasibility of the model. Only lung metastases are linked to the RT schedule and the timing of surgery (no differences in metastases are observed in the other organs). Lung metastases are less important in size and less frequent in the hypofractionated RT schedule (10Gy/5Gy) as compared to the conventional one. Moreover, in the 10Gy/5Gy, when surgery is performed at 11 days after the end of RT, the size and the number of lung metastases are smaller compared to 4 days. Inversely, in the 10Gy/2Gy schedule, applying surgery at 4 days protects the mice against lung metastases compared to surgery at 11 days. Tumor volumes are the same in all groups and cannot be incriminated in the difference of lung metastases occurrence. Neither MMP's, nor HIF-1 expression change significantly between groups and cannot be correlated to the number of lung metastases. Only cytokine array shows a significant different profile between the RT schedules.

Conclusions:

We have established a pre-clinical model of neoadjuvant RT followed by surgery enabling us to study the impact of neoadjuvant RT schedules and the timing of surgery on tumor dissemination. We report here that both dose per fraction and timing of the surgery influence the occurrence of lung metastases. The underlying mechanisms are still not fully understood. Modeling neoadjuvant RT in such a setting offers new opportunities to develop therapeutic strategies to improve cancer treatment.